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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/030,203 | 12/31/2001 | Alan Garen | OCR-679B.US | 9075 |

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| EXAMINER | |
|---|---|
| BLANCHARD, DAVID J | |
| **ART UNIT** | **PAPER NUMBER** |
| 1642 | |

DATE MAILED: 11/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/030,203 | GAREN ET AL. | |
| | Examiner | Art Unit | |
| | David J Blanchard | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-3,6-14,17-19,21,23,35,36,38,46,49 and 54-57* is/are pending in the application.

4a) Of the above claim(s) *9-14, 17-19, 23, 35-36, 38 and 49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 6-8, 21, 46 and 54-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/3/04; 7/7/04;* 8/4/04; 10/7/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 4-5, 15-16, 20, 22, 24-34, 37, 39-45, 47-48 and 50-53 have been cancelled.

Claims 1-3, 6-8, 21 and 46 have been amended.

Claims 54-57 have been added.

2. Claims 1-3, 6-8, 21, 46 and 54-57 are under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Rejections.

***Objections/Rejections Withdrawn***

5. The objection to the specification for containing embedded hyperlinks and other form of browser-executable code is withdrawn in view of the amendments to the specification filed 8/16/2004.

6. The rejection of claims 1, 3, 6-8 and 47 under 35 U.S.C. 102(b) as being anticipated by Nakagaki et al is withdrawn in view of Applicant's arguments and amendments to then claims.

7. The rejection of claim 47 under 35 U.S.C. 102(b) as being anticipated by Nakagaki et al is withdrawn in view of the cancellation of claim 47.

8. The rejection of claims 1-3, 6-8 and 46-47 under 35 U.S.C 103(a) as being unpatentable over Olson et al in view of Drake et al and Contrino et al and Dickinson et

al and Berkner et al is withdrawn in view of Applicant's arguments and amendments to the claims.

9. The rejection of claims 1-3, 6-8, 21-22 and 46-47 under 35 U.S.C 103(a) as being unpatentable over Thorpe et al in view of Min et al and Contrino et al and Dickinson et al and Berkner et al is withdrawn in view of Applicant's arguments and amendments to the claims.

***New Grounds of Rejections***

10. Claim 21 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. Base claim 1 from which claim 21 depends recites that the effector domain is an Fc region of a human IgG1 immunoglobulin and the targeting domain is a mutant form of factor VII. Therefore, claim 21 does not further limit the subject matter of base claim 1 because claim 21 is broadly drawn to any "effector domain" and any "tageting domain", not necessarily the Fc of a human IgG1 immunoglobulin and a mutant form of factor VII, respectively.

11. Claims 1-3, 6-8, 21, 46 and 54-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1-3, 6-8, 21, 46 and 54 are indefinite for reciting an immunoconjugate protein comprising an "Fc region of a human IgG1 immunoglobulin" in claim 1 and "a dimmer of two identical chains" in claim 21. The claims are unclear because an Fc region is comprised of two identical C-terminal heavy chain segments linked by disulfide bonds and noncovalent forces (i.e., dimmer of two identical chains as evidenced by Cruse et al, Illustrated Dictionary of Immunology, CRC Press, page 109, 1995). Thus, it is unclear if the claims are drawn to an immunoconjugate comprising a mutant form of factor VII conjugated to a dimeric Fc region (i.e., two C-terminal heavy chain segments linked by disulfide bonds and noncovalent forces), wherein the immunoconjugate forms a dimer having two identical polypeptide chains, each comprising a mutant form of factor VII conjugated to a dimeric Fc region or does the immunoconjugate comprise one C-terminal heavy chain segment conjugated to a mutant form of factor VII, wherein two identical chains form a dimer?

b. Claims 55-57 recite the limitation "the mutant form of human factor VII" in claims 55-57. There is insufficient antecedent basis for this limitation in the claim because base claim 1 recites "a mutant form of factor VII", and not human factor VII.

c. Claims 55-57 are indefinite for reciting "is native factor VII". It is unclear if the phrase "native factor VII" refers to human factor VII or some other factor VII (i.e., mouse factor VII) because base claim 1 from which claims 55-57 depend does not recite that factor VII is human factor VII.

12. Claims 1-3, 6-8, 21, 46 and 54-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunoconjugate protein comprising an Fc region of a human IgG1 immunoglobulin conjugated to a targeted domain comprising a mutant from of factor VII, wherein the immunoconjugate binds tissue factor, does not reasonably provide enablement for an immunoconjugate protein comprising an Fc region of a human IgG1 immunoglobulin conjugated to a targeted domain comprising a mutant from of factor VII, wherein the immunoconjugate does not bind tissue factor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to an immunoconjugate protein comprising an Fc region of a human IgG1 immunoglobulin conjugated to a targeted domain comprising a mutant from of factor VII comprising one or two mutations selected from the group consisting of a substitution of alanine fro lysine-341, and a substitution of alanine for serine-344 and the immunoconjugate further comprises a cytotoxic radioactive tag. The specification

teaches immunoconjugates comprising tissue factor VII conjugated to an Fc region of a human IgG1 immunoglobulin comprising a substitution of alanine for lysine-341 and a substitution of alanine for serine-344 and the immunoconjugate binds tissue factor. The specification has not taught immunoconjugates comprising tissue factor VII conjugated to an Fc region of a human IgG1 immunoglobulin comprising a substitution of alanine for ~~fro~~ lysine-341 and a substitution of alanine for serine-344 and the immunoconjugates do not bind tissue factor.

The specification does not teach how to make or use immunoconjugates comprising the claimed variant factor VII proteins, which encompasses any mutant form of factor VII that binds tissue factor. This does not provide sufficient, specific guidance, enabling the skilled artisan to make and/or use the invention without undue experimentation. The specification does not disclose the extremely large number of mutant forms of factor VII broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar biological activity are limited in any protein. The result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g., multiple substitutions. The sequence of some proteins is highly conserved and one

skilled in the art would not expect tolerance to any amino acids modifications in such proteins. The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does not disclose the following:

a. The general tolerance to modification and extent of such tolerance;

b. The specific positions and regions of the sequence which can be predictably modified and which regions are critical;

c. What fragments, if any, can be made which retain the biological activity of the intact protein; and

d. The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in a manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions, or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the protein's structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).f.

Furthermore, protein chemistry is probably one of the most unpredictable areas of biotechnology. Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79:1979-1983, 1982) teaches that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

Lederman et al (Molecular Immunology 28:1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document).

Li et al (Proc. Natl. Acad. Sci. USA 77:3211-3214, 1980) disclose that dissociation of immunoreactivity from other activities when constructing analogs (see entire document).

Coleman P. M. (Research in Immunology, 145:33-36, 1994) discloses that even single amino acid changes within the interface of an antibody-antigen complex can alter the interaction by driving the affinity towards more tightly bound complexes or effectively abolish the interaction entirely (see page 33).

Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art. The art of protein chemistry remains very unpredictable as Rudikoff et al, Lederman et al, Li et al and Coleman P. M. conclusively demonstrate.

In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad mutant forms of factor VII as a targeting domain of an immunoconjugate as encompassed by the scope of the claims,

one skilled in the art would be forced into undue experimentation in order to practice the claimed invention.

Applicant may obviate this rejection by amending the claims to recite that the immunoconjugate protein binds tissue factor.

***Conclusions***

13. No claim is allowed.

14. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571)

272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D
PRIMARY EXAMINER